**Title**: Neurodevelopmental features among infants with congenital hypotonia: An observational cross-sectional study.

**Authors**: Patricio Barría1,2, Matías Castillo-Aguilar3,4, Katherine Harris3,4, Kay Gittermann1,5, Mónica Bontes1, Rolando Aguilar1,6, Carlos A. Cifuentes7,8, Marcela Munera9, Cristian Núñez-Espinosa4,10\*

1 Corporación de Rehabilitación Club de Leones Cruz del Sur, Punta Arenas, Chile.

2 Brain-Machine Interface Systems Lab, Universidad Miguel Hernández de Elche, Elche, España.

3 Kinesiology Department, Magallanes University, Punta Arenas, Chile.

4 Centro Asistencial de Docencia e Investigación (CADI-UMAG), Punta Arenas Chile.

5 Hospital Clínico de Magallanes, Punta Arenas, Chile.

6 Engineering Department, Magallanes University, Punta Arenas, Chile.

7 Bristol Robotics Laboratory, University of the West of England T Block, Frenchay Campus.

8 School of Engineering, Science and Technology, Universidad del Rosario, Bogota, Colombia.

9 Department of Biomedical Engineering, Colombian School of Engineering Julio Garavito.

10 School of Medicine, Magallanes University, Punta Arenas, Chile.

### \*Autor de correspondencia

Cristian Núñez-Espinosa, School of Medicine, Magallanes University, Punta Arenas, Chile. Centro Asistencial de Docencia e Investigación CADI-UMAG, Chile. e-mail: [cristian.nunez@umag.cl](mailto:cristian.nunez@umag.cl). Address: Avenida Bulnes 01855, Box 113-D. Phone: +56 61 2201411

## Abstract

**Objective**: To describe and model the relationship between sociodemographics, prematurity and neurodevelopmental levels based on the *Ages and Stages Questionnaire* (ASQ-3) scores in infants diagnosed with congenital hypotonia (CH). **Method**: A total of 229 patients diagnosed with CH participated in this study (median age, 8 years; 93 (40.6%) females and 136 (59.4%) males). Neurodevelopmental status was assessed with the ASQ-3 at admission, as well as sociodemographic and obstetric data obtained through the initial clinical interview. **Results**: When modeling the neurodevelopmental status of each domain, an overall negative effect of corrected age on communication and problem-solving skills was observed, whereas the overall effect tends to be positive in gross motor function. Fine motor skills did not exhibit a linear relationship but a non-linear effect with corrected age, unlike the personal-social domain, which did not present significant variations across age corrected for prematurity. **Conclusion**: After adjusting for possible confounders, we found between-subjects fluctuations in neurodevelopmental traits across age in hypotonic infants. These fluctuations were present in the form of non-linear and domain-specific variations.

What this paper adds:

* Describes the levels of variations observed in neurodevelopmental traits across age in hypotonic infants.
* Provides the estimated probability of developmental delay according to the ASQ-3 across age in hypotonic infants.
* The variations observed in developmental domains are not solely attributable to prematurity, where age corrected for prematurity best explains the variability observed in neurodevelopment.

**Keywords**: Developmental traits, Congenital hypotonia, Ages and Stages Questionnaire (ASQ), Infants.

Early childhood development’s physical and psychological signs are representative and relevant markers for identifying and monitoring overall growth in early life ([1](#ref-di2016predictive)). Therefore, both can be used in screening children at risk of developmental delay to support early referral and identify the need for further assessment to determine if they are eligible for early intervention services ([2](#ref-bruder2010early),[3](#ref-guralnick2017early)).

Currently, many tools have been proposed to assess the continued development of infants. In this sense, the Ages and Stages Questionnaire, Third Edition (ASQ-3), has been presented as a global screening tool aimed at parents/caregivers, assessing five developmental domains in children aged 0 to 5.5 years ([4](#ref-singh2017ages)). Current evidence suggests that the ASQ-3 is an accurate, cost-effective, and parent-friendly instrument for screening and monitoring children through pre-school age, helping to identify and prevent neurodevelopmental deficits in children born very premature ([4](#ref-singh2017ages)–[6](#ref-ballantyne2016risk)).

Multiple neuromuscular, metabolic, and genetic conditions have been associated with hypotonia. Hypotonia is the decreased muscle tone or flaccidity and may represent a sign of delayed neurological development in the child, which may predispose to cognitive impairment in some cases ([7](#ref-riou2009global)). Because the baby’s growth-associated hypotonia, hypermobility, and motor delay can affect her ability to relate to her environment, critical visual cues are not always interpreted, leading to impaired learning and cognitive development ([8](#ref-harris2008congenital)). Hypotonia implies a wide range and levels of muscle flaccidity, which should be explored in the cognitive development of the infant ([8](#ref-harris2008congenital),[9](#ref-gabis2021weak)). There are multiple causes of hypotonia, one of them being congenital hypotonia (CH). Some authors suggest that CH cannot be referred to as a diagnosis ([10](#ref-thompson2002benign)). Those who do consider it point it out as a diagnosis of exclusion, considering it only when it is established in the absence of other signs and symptoms ([9](#ref-gabis2021weak),[11](#ref-leyenaar2005schematic)). However, its research is fundamental since it is a non-progressive neuromuscular disorder, which tends to improve with early intervention ([9](#ref-gabis2021weak)).

To our knowledge, there is no substantial evidence characterizing the variations in developmental traits in infants with diagnosed CH across ages. Therefore, our primary goal in this study was to describe and model the relationship between prematurity, and neurodevelopmental levels assessed through ASQ-3 as a function of age in infants diagnosed with CH.

# Material y methods

## Ethics

Participating subjects gave their permission, and legal guardians provide informed consent before participation. The Ethics Committee approved this study of the Corporación de Rehabilitación Club de Leones Cruz del Sur, Chile (code: CorporacionRCLCS010322), following the regulations established by the Declaration of Helsinki on ethical principles in human beings.

## Study design

We conducted an observational, cross-sectional study under a quantitative approach.

## Participants

A total of 229 patients were enrolled as part of an intervention program carried out by the Cruz del Sur Rehabilitation Center (Punta Arenas, Chile), admitted from one month to 35 months old, and evaluated at admission, control and discharge. Participating patients were diagnosed based on clinical criteria confirmed by a neurologist and a physiatrist. The total files of the patients diagnosed with CH, and admitted to the institution’s program, were analyzed, and the evaluation of the subjects was carried out and guided by a nurse trained in the application of the ASQ-3.

In this context, it is worth noting that the data, as well as the patient registry, are part of institutional strategies aimed at the diagnosis and continuous monitoring of the clinical situation of users, which are used to improve care processes and clinical decision-making.

The diagnosis of CH is based on four sources: 1) primary care pediatrician, who refers the diagnosis to the institution where admission to the program is made; 2) pediatricians from private clinics, who refer the diagnosis; 3) neuropediatricians from the clinical hospital, who refer the diagnosis to the program; 4) physiatrist from the institution, who assigns the diagnosis if it corresponds to the semiology.

## Measures

### The Ages and Stages Questionnaire, third edition (ASQ-3)

The ASQ-3 is a parent-reported initial level developmental screening instrument consisting of 21 intervals, each with 30 items in five areas: i) communication (CM), ii) gross motor (GM), iii) fine motor (FM), iv) problem-solving (CG), and v) personal-social (PS) ([12](#ref-squires2009ages)). The ASQ is cost-effective and widely used in the United States and other countries ([13](#ref-heo2008cross),[14](#ref-sarmiento2011universal)). It has been translated into several languages, and international studies on its psychometric properties in diverse cultural environments are increasing ([13](#ref-heo2008cross),[14](#ref-sarmiento2011universal)). It has shown good psychometric properties (75% sensitivity and 81% specificity) in Chilean term and preterm infants ([15](#ref-schonhaut2013validity)).

## Procedures

For the collection of research data, authorization consent was obtained for the use of instrumental clinical data as well as the clinical record of each patient. Subsequently, and following national research regulations, written authorization was obtained from the institutional director to use the forms and database for research purposes. To this end, the data were anonymized during data processing and subsequent analyses.

### Collection of demographic data

Each patient’s demographic data were collected and made available throughout the study by the institutional electronic systems at the time of entry to the program. The administrative registration was done by the secretaries of the user coordination unit, recording name, ID number, date of birth and diagnosis. In addition, age data was automatically updated by the computer system’s algorithms.

### Assessment with ASQ-3

The ASQ-3 was applied according to the protocol established by the instrument itself, with a face-to-face or telematic application being valid. The protocol can be found in the instrument’s manuals, which the program nurse administered. Some important considerations of the administration are that i) the primary caregiver must answer, ii) in case of doubts of the caregiver about the assessed behavior, the information is corroborated by in situ tests with the user, and iii) in relation to the correction, the test itself standardizes these procedures.

## Statistical analysis

Data are presented as median (*Mdn*) and interquartile range (*IQR*) for continuous variables; for categorical/discrete variables, the absolute and relative sample size was reported. There was no missing data.

A non-parametric approach was used since the underlying distribution of continuously measured outcomes, assessed through analytical and graphical methods, did not follow a Gaussian distribution.

In order to assess the differences in developmental scores between males and females, the *Wilcoxon* rank-sum test was used, meanwhile the chi-square test () was used to evaluate goodness-of-fit ().

Generalized additive models (GAM) were used to describe linear and non-linear relationships in the form of smooth terms between developmental characteristics, represented through penalized regression splines ([16](#ref-wood2011fast)). The restricted maximum likelihood method was used to estimate the smoothing parameters, and thin-plate regression splines as the smoothing basis, as they are the optimal smoother of any given basis dimension/rank ([17](#ref-wood2003thin)). We used approximative derivatives with 95% confidence intervals (CI95%) to describe the smooth terms by means of quasi-linear segments ([18](#ref-dominique2020estimation)).

In order to assess the influence of confounding variables, we fitted different models using the categorical variables: i) sex of the infant, ii) clinician ID and iii) the relationship of the infant to the respondent (i.e., whether the respondent was the infant’s mother, father, uncle or grandparent) as random effects in the form of penalized parametric terms ([19](#ref-wood2016smoothing)). Varying random effects structures and model performance metrics can be seen in the supplementary file.

Based on the technical report of the ASQ-3, we’ve been able to estimate the threshold of possible delay based on the total score for each developmental domain. Within this framework, a logistic regression was used to estimate the predicted probability of a developmental delay given the corrected age for each domain.

A probability of committing a type I error of less than 5% was considered sufficient evidence for null hypothesis significance testing. All the statistical analyses were computed and implemented in the R programming language ([20](#ref-rlanguage)). GAMs and the corresponding model estimates were calculated using the *mgcv* and *modelbased* packages ([18](#ref-dominique2020estimation),[21](#ref-wood2017generalized)). Complementary R packages were used for visualization purposes ([22](#ref-daniel2021see),[23](#ref-hadley2016ggplot2)).

# Results

From a total of 229 subjects with congenital hypotonia, 93 (40.6%) were females and 136 (59.4%) males ( (1) = 8.07, *p* = 0.004). The developmental characteristics of the sample can be seen in [Table 1](#tab1).

## Neurodevelopment as a function of corrected age

When modeling the effect of chronological age on developmental domains, different random effects structures were compared when assessing model estimates, these estimates can be seen in [Figure 1](#fig1).

### Communication

After fitting a GAM to assess the effect of corrected age on CM scores, we observed a significant non-linear relationship between them ( (4.81, 219.93) = 15.39, *p* < 0.001), that reflect an overall negative marginal trend ( = -2.06, CI95%[-3.32, -0.8], (219.93) = -3.23, *p* = 0.001), however, this was not true when assessing the direction of the effect in the age range between 0 to 6.7 ( = 0.57, CI95%[-1.01, 2.16], (219.93) = 0.43, *p* = 0.288), neither in the 17.3 to 35 months old group ( = 0.2, CI95%[-1.7, 2.11], (219.93) = 0.16, *p* = 0.677), whereas the effect tend to be positive but non-significant. The relationship between developmental domains, corrected age and their effect derivatives can be seen in [Figure 2](#fig2).

### Gross motor

When analyzing the motor skills domain, we found a significant non-linear effect of corrected age on GM scores, (4.75, 222.3) = 6.31, *p* < 0.001, which had an overall positive effect ( = 1.77, CI95%[0.31, 3.24], (222.3) = 2.38, *p* = 0.018), however, the slope varied as a function of age, with a negative effect in the 0 to 6.7 age range ( = -3.14, CI95%[-4.99, -1.3], (222.3) = -3.5, *p* = 0.005), but in the 10.3 to 15.2 interval, this relationship was inverted ( = 1.9, CI95%[0.42, 3.38], (222.3) = 2.53, *p* = 0.015), however, in the rest of the age range the slope was non-significant and virtually zero (Age[7.1, 9.9], = 0.27, CI95%[-1.11, 1.66], (222.3) = 0.32, *p* = 0.369; Age[15.6, 35], = 0.24, CI95%[-1.92, 2.4], (222.3) = 0.29, *p* = 0.763).

### Fine motor

Although a similar non-linear effect wasn’t observed when inspecting the influence of corrected age in the FM domain scores on the global test statistics ( (2.56, 228.03) = 4.11, *p* = 0.006), and neither was possible to estimate a significant overall effect different from zero ( = 0.01, CI95%[-0.47, 0.49], (228.03) = 0.03, *p* = 0.977), nevertheless, it was only in the 23 to 28.3 age range where a significant and negative effect was observed ( = -0.8, CI95%[-1.55, -0.04], (223.23) = -2.09, *p* = 0.038).

### Problem solving

CG abilities were significantly influenced by corrected age ( (5.28, 220.66) = 4.18, *p* < 0.001), with an overall negative effect ( = -1.99, CI95%[-3.5, -0.48], (220.66) = -2.6, *p* = 0.01), and just like the other domains, this relationship was modified across the corrected age. In this sense, from the 0 to 5.7 age interval, we found that for every increase in one month in corrected age, we can expect a proportional increase in 2.94 points ( = 2.94, CI95%[1, 4.88], (220.66) = 3.11, *p* = 0.007) in the CG domain, while in the age range 9.5 to 13.4 the relationship changes inversely, mainly because in this age range we observe that for every one-month increase in the corrected age, a decrease of 1.93 points could be expected in the same domain ( = -1.93, CI95%[-3.44, -0.41], (220.66) = -2.51, *p* = 0.017). The other age intervals did not have a slope that deviated significantly from zero (Age[6, 9.2], = -0.08, CI95%[-1.45, 1.29], (220.66) = -0.08, *p* = 0.358; Age[13.8, 35], = -0.16, CI95%[-2.34, 2.01], (220.66) = -0.18, *p* = 0.507).

### Personal-social

Unlike the others, the PS domain was not influenced by corrected age ( (1, 225.36) = 0.99, *p* = 0.321), given that the marginal effect across age was virtually zero ( = -0.09, CI95%[-0.28, 0.09]).

## Prematurity

Accordingly, prematurity (measured in weeks) was not associated with any non-linear variations in neurodevelopmental domains within ASQ-3 assessment (significance for smooth terms: CM, *p* = 0.594; FM, *p* = 0.901; GM, *p* = 0.342; CG, *p* = 0.371; PS, *p* = 0.172).

## Risk of developmental delay and corrected age

When analyzing the probability of having a developmental delay based on the scores for each domain, we found a significant non-linear effect for CM ( (2.83) = 27.71, *p* < 0.001), whereas in this domain we observed that for every one-month increase in the corrected age in the 9.9 to 31.1 age range, the odds of a possible developmental delay increases by 20% (OR = 1.2, CI95%[1.05, 1.37], (223.84) = 2.83, *p* = 0.01). Similar to CM, an overall linear effect of corrected age in the GM domain was observed ( (1) = 8.88, *p* = 0.003), whereas for every one-month increase the odds of a possible developmental delay decrease by a 5% (OR = 0.95, CI95%[0.92, 0.98], (227) = -2.98, *p* = 0.003). The probability associated with a possible delay according to the total score for each developmental domain in response to corrected age can be observed in [Figure 3](#fig3).

# Discussion

The objective of our investigation was to elucidate and conceptualize the association between prematurity and neurodevelopmental functioning, evaluated through the Ages and Stages Questionnaires-Third Edition (ASQ-3), as a function of age in infants diagnosed with congenital heart disease (CH). Our principal discoveries indicate a curvilinear influence of age, which was adjusted for prematurity, resulting in a significant reduction of essential neurodevelopmental characteristics at distinct age intervals, while accounting for the impact of caregiver rapport, gender, and inter-rater bias. However, no fluctuation was detected in the PS domain across the adjusted age.

These findings confirm the described motor impairments of hypotonia in the early stages of life, which compromise the infant’s ability to explore and interact with their environment ([8](#ref-harris2008congenital),[9](#ref-gabis2021weak)). The limitations in GM function during the early stages of life are expected to result in impaired FM skills during subsequent developmental stages. Consequently, these deficiencies may negatively impact the communicative capabilities of infants, as their interaction and engagement with their environment and peers would be reduced. ([24](#ref-bodensteiner2008evaluation)). In a recent systematic review ([25](#ref-gonzalez2019gross)), differences in the predictive abilities of gross and FM skills on communication skills in infants and early childhood were reported. Whereas GM skills, such as crawling and walking, favor exploration with their environment and caregivers, while FM skills, expressed through tasks such as drawing and handling utensils, could lead to improvements in language through mechanisms yet to be explored ([25](#ref-gonzalez2019gross)). These milestones may be impaired in the face of poorer head and trunk control in CH, which have been shown to delay the achievement of crucial motor milestones in infants ([8](#ref-harris2008congenital),[9](#ref-gabis2021weak),[24](#ref-bodensteiner2008evaluation)).

It is worth noting that other context-mediated social factors may also have influenced our results, mainly due to the role that other variables would also play in the neurodevelopment of our study sample, which could have an impact on many of the developmental traits assessed here, such as intrauterine growth restrictions, maternal depression, institutionalization, exposure to social violence, maternal education and breastfeeding ([26](#ref-walker2011inequality)). Altogether, these represent the main limitations in our study design, which need to be addressed in future research, exploring the variations observed in different developmental traits in hypotonic infants. However, our study sheds light on an underexplored aspect with robust statistical methods that enabled us to capture and model the complex relationships seen early in life.

# Conclusion

The present study shows that the marked variations observed in neurodevelopmental traits are present across age in hypotonic infants, mainly in the form of non-linear and domain-specific variations, even after adjusting for the effect that caregiver relationship, sex and evaluators might exert. Moreover, we show that the observed variations in developmental domains are not solely attributable to prematurity, where age corrected for prematurity best explains the observed variability in neurodevelopment. Future research may determine how these findings apply when controlling for context-mediated social factors and other clinical populations.

# Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

# Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

# Conflicts of interest

The authors declare that the research was conducted without any commercial or financial relationships construed as a potential conflict of interest.

# ORCID

Patricio Barría, 0000-0003-4088-9820

Matías Castillo-Aguilar, 0000-0001-7291-247X

Katherine Harris, 0000-0003-4271-6405

Kay Gittermann, 0000-0002-8042-844X

Mónica Bontes, 0000-0002-0592-7361

Rolando Aguilar, 0000-0002-0104-3032

Carlos Cifuentes, 0000-0002-6942-865X

Marcela Munera, 0000-0001-6595-5383

Cristian Núñez-Espinosa, 0000-0002-9896-7062

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